

MSH2 gene

mutS homolog 2

Normal Function

The *MSH2* gene provides instructions for making a protein that plays an essential role in repairing DNA. This protein helps fix errors that are made when DNA is copied (DNA replication) in preparation for cell division. The MSH2 protein joins with one of two other proteins, MSH6 or MSH3 (each produced from a different gene), to form a two-protein complex called a dimer. This complex identifies locations on the DNA where errors have been made during DNA replication. Another group of proteins, the MLH1-PMS2 dimer, then binds to the MSH2 dimer and repairs the errors by removing the mismatched DNA and replicating a new segment. The *MSH2* gene is one of a set of genes known as the mismatch repair (MMR) genes.

Health Conditions Related to Genetic Changes

Constitutional mismatch repair deficiency syndrome

About 10 variants (also known as mutations) in the *MSH2* gene have been associated with a condition called constitutional mismatch repair deficiency (CMMRD) syndrome. Individuals with this condition are at increased risk of developing cancers of the colon (large intestine) and rectum (collectively referred to as colorectal cancer), brain, and blood (leukemia or lymphoma). These cancers usually first occur in childhood, with the vast majority of cancers in CMMRD syndrome diagnosed in people under the age of 18. Many people with CMMRD syndrome also develop changes in skin coloring (pigmentation), similar to those that occur in a condition called neurofibromatosis type 1.

Individuals with CMMRD syndrome inherit two *MSH2* gene variants, one from each parent, while people with Lynch syndrome (described below) have a variant in one copy of the *MSH2* gene.

MSH2 gene variants result in near or complete loss of MSH2 protein production. A shortage of this protein eliminates mismatch repair activity and prevents the proper repair of DNA replication errors. These errors accumulate as the abnormal cells continue to divide. The errors disrupt other genes involved in important cellular processes, such as controlling cell growth and division (proliferation). If cell growth is uncontrolled, it can lead to childhood cancer in people with CMMRD syndrome.

It is thought that the features of neurofibromatosis type 1 in people with CMMRD syndrome are due to genetic changes in the *NF1* gene that result from loss of mismatch repair. These changes are present only in certain cells (somatic variants), whereas *NF1* gene variants that are present in all cells of the body cause neurofibromatosis type 1.

Lynch syndrome

About 20 percent of all cases of Lynch syndrome with an identified gene variant are associated with inherited variants in the *MSH2* gene. Lynch syndrome increases the risk of many types of cancer, particularly colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the endometrium (lining of the uterus), ovaries, stomach, small intestine, gallbladder ducts, upper urinary tract, and brain. By age 75, the risk of developing one of these cancers is 80 percent for women and 75 percent for men with an *MSH2* gene variant.

MSH2 gene variants involved in Lynch syndrome may cause the production of an abnormally short or inactive MSH2 protein or prevent the production of any protein from one copy of the gene. An altered protein cannot perform its normal function. A decrease in functional MSH2 protein leads to an increase in unrepaired DNA errors during cell division. The errors accumulate as the cells continue to divide, increasing the risk of tumor formation in the colon or another part of the body.

Because there is some functional MSH2 protein produced from the normal copy of the gene, mismatch repair activity in Lynch syndrome is reduced but not absent, as it is in CMMRD syndrome (described above). This difference in DNA repair activity levels likely explains why cancers in Lynch syndrome generally develop in adulthood while those in CMMRD syndrome often affect children.

Some variants in the *MSH2* gene cause a form of Lynch syndrome called Muir-Torre syndrome. In addition to colorectal cancer, people with this condition have an increased risk of developing several uncommon skin tumors. These rare skin tumors include sebaceous adenomas and carcinomas, which occur in glands that produce an oily substance called sebum (sebaceous glands). Multiple rapidly growing tumors called keratoacanthomas may also occur, usually on sun-exposed areas of skin.

Ovarian cancer

Inherited changes in the *MSH2* gene increase the risk of developing ovarian cancer, as well as other types of cancer, as part of Lynch syndrome (described above). Females with Lynch syndrome have an 8 to 10 percent chance of developing ovarian cancer, as compared with 1.6 percent in the general population.

Other Names for This Gene

- MSH2_HUMAN
- mutS (E. coli) homolog 2
- mutS (E. coli) homolog 2 (colon cancer, nonpolyposis type 1)
- mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MSH2 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4436\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4436[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28MSH2%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>)

Catalog of Genes and Diseases from OMIM

- MUIR-TORRE SYNDROME; MRTES (<https://omim.org/entry/158320>)
- MutS HOMOLOG 2; MSH2 (<https://omim.org/entry/609309>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/4436>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=MSH2\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=MSH2[gene]))

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Genomic Location

The *MSH2* gene is found on chromosome 2 (<https://medlineplus.gov/genetics/chromosome/2/>).

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